Numb Chin Syndrome: A Rare and Often Overlooked Symptom

Alexandre T. Assaf, MD, DMD
Consultant, Department of Oral and Maxillofacial Surgery
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Tim P. Jürgens, MD
Consultant, Department of Systems Neuroscience and Headache Clinic
Department of Neurology
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Andreas W. Benecke, DMD
Resident, Department of Prosthodontics
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Björn Riecke, MD, DMD
Consultant, Department of Oral and Maxillofacial Surgery
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Marco Blessmann, MD, DMD, PhD
Senior Consultant, Department of Oral and Maxillofacial Surgery
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Tomislav A. Zrnc, MD
Resident, Department of Oral and Maxillofacial Surgery
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Chressen C. Much, MD
Resident, Department of Radiology
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Max Heiland, MD, DMD, PhD
Professor and Head, Department of Oral and Maxillofacial Surgery
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Reinhard E. Friedrich, MD, DMD, PhD
Professor and Senior Consultant
Department of Oral and Maxillofacial Surgery
University Medical Center Hamburg Eppendorf, University of Hamburg
Hamburg, Germany

Correspondence to:
Dr Dr Alexandre Thomas Assaf
Department of Oral and Maxillofacial Surgery
University Medical Center Hamburg Eppendorf
Martinistr. 52, 20246, Hamburg, Germany
Fax: +49.40.74.10.55.467
Email: a.assaf@uke.uni-hamburg.de

Numb chin syndrome (NCS) describes a sensory neuropathy characterized by numbness in the distribution of the terminal branch of the mandibular division of the trigeminal nerve. Benign as well as malignant diseases are known to cause NCS. This is often misdiagnosed, and in some cases the symptom may lead to a late detection of malignancy. Reports of 10 cases in which NCS was the presenting and isolated symptom, caused by extracranial malignancies, drugs, or dental/surgical interventions, are presented. This article outlines the symptoms and the diagnostic approaches taken, provides a short review of the etiology and pathogenesis, and proposes diagnostic criteria and treatment of NCS. Both medical practitioners and dentists need to be aware of the relationship between malignancies and paresthesia of the chin or complete loss of sensation in partial segments of the jaw. In addition, dentists should be aware of the diagnostic limitations of an orthopantomogram to detect underlying diseases beyond localized dental disorders. *J Oral Facial Pain Headache 2014;28:80–90. doi: 10.11607/jop.994*

Key words: *bisphosphonate-related osteonecrosis of the jaw (BRONJ), dental implant, iatrogenic, metastasis, multiple sclerosis, neuropathy, numb chin syndrome*

Numb chin syndrome (NCS) describes a sensory neuropathy characterized by numbness (hypoesthesia, paresthesia, dysesthesia, anesthesia) in the distribution of the terminal branch of the mandibular division of the trigeminal nerve,[1] which can affect the skin of the lips and chin, the gingiva, and the teeth.[2–4] Cases of NCS were reported in the 19th century by Bell and Vincent in patients with mandibular injuries or retromandibular tumors.[5–7] Most cases of NCS, however, are caused by nerve damage occurring during dental and maxillofacial therapies including mandibular block,[8–10] as well as odontogenic pathologies (such as dental abscesses or osteomyelitis). Indeed, the spectrum of underlying pathologies is large and includes both localized and systemic pathologies: multiple sclerosis[11,12] and other neuropathies, temporal arteritis,[13] blood disease,[12,14] benign osseous pathologies,[12,15] diabetes,[12] sarcoidosis,[12] syphilis,[12] leptomeningeal invasion,[16] benign or malignant tumors, and drugs (eg, bisphosphonates) (Table 1).[16] The number of bisphosphonate-induced NCS cases has increased in recent years following the more widespread long-term use of this medication. It should be noted that in the absence of a history of maxillofacial trauma, dental procedures, or local bony pathologies, the nerve damage is more often caused by a malignancy than a nonmalignancy and the NCS can be the first symptom of a metastasis.[11–14] Therefore, a NCS must always be taken seriously by dentists, and investigations for the detection of a possible malignancy are mandatory.[15–25]

In patients with a metastasis-related NCS, the primary tumor is most often localized to the breast, lung, kidney, thyroid, prostate, or stomach (Table 1).[15,23] Most cases with distant metastasis from these organs to the mandible are associated with late and more often fatal stages of the malignant disease.[15,18] Other, but rarely occurring,

Table 1 Etiology and Pathogenesis of Numb Chin Syndrome (NCS)

Nonmalignant causes of NCS		Malignant causes of NCS
Dental causes or iatrogenic in origin	Systemic causes	
Dental abscess	Diabetes mellitus	Breast cancer
Extraction of wisdom teeth	Aneurysms	Lung cancer
Osteomyelitis	Amyloidosis	Hematological malignancy
Benign tumor	Sickle cell anemia	Head and neck cancer
Sensory disruption after inferior dental nerve block	HIV	Lymphoma
Implants	Multiple sclerosis	Renal tumor
Mandibular surgery	Lyme disease	Melanoma
Orthognathic surgery of the mandible	Vasculitis	Gastrointestinal cancer
Facial trauma	Sarcoidosis	Multiple myeloma
Orthodontic treatment (due to excess pressure)	Syphilis	Brain cancer
Faulty dentures (compressing mental foramen during mastication)	Demyelinating disorder	Prostate cancer
Endodontic treatment (mechanical/chemical injury to inferior alveolar nerve – less common)		

tumors with metastasis-related NCS are multiple myeloma,[26] ovarian carcinoma,[25] mucoepidermoid carcinoma,[27] mediastinal small-cell carcinoma,[15] Burkitt lymphoma,[28–30] and acute leukemia.[31]

Following are reports of 10 patients who presented with NCS as an isolated symptom of different etiologies, including malignancies, dental treatment, and bisphosphonate therapy.

Case Reports

A retrospective study was carried out in which the medical charts of patients who attended the Department of Oral and Maxillofacial Surgery; the Department of Systems, Neuroscience and Headache Clinic, Department of Neurology; and the Department of Prosthodontics (University Medical Center Hamburg Eppendorf, Germany) were analyzed to find patients with NCS as an isolated symptom. In a period of almost 3 years (October 2007 to December 2010), 10 patients, 5 men and 5 women, were identified (8 patients in the Department of Oral and Maxillofacial Surgery, 1 patient in the Department of Neurology, and 1 patient in the Department of Prosthodontics). All patients received different types of clinical and radiologic examinations that ultimately led to the diagnosis and final detection of the underlying cause. All these cases were from consecutive patients referred for NCS during that period of 3 years.

The clinical examination included a standardized examination protocol used in all the departments. The assessment of tooth vitality and occlusal disturbances were performed in the Department of Oral and Maxillofacial Surgery and Department of Prosthodontics. All patients were examined for tooth vitality, dental sensitivity to cold, tenderness on percussion, mucositis, periodontitis, bilateral sign of dental and mucosal sensory deficit (hypoesthesia, paresthesia, dysesthesia or anesthesia), as well as restrictions of mandibular movements. A neurologic examination included a comprehensive assessment of the three branches of the trigeminal nerve. Patients were tested for hypoesthesia by touching the facial skin including the upper and lower lip with a wooden spatula, for allodynia with a cotton swab, for punctuate sensations with a pinprick, and for thermal sensations with two test tubes filled with hot and cold water, respectively. In addition, the integrity of trigeminally innervated muscles was ascertained by testing masseter muscular power.

In all patients, biopsy specimens were taken intraoperatively and were analyzed in the Institute of Pathology (Table 2).

The study was not approved by the local ethics committee. Approval by the local institutional review board was not necessary for this case series.

Case 1

In January 2009, a 65-year-old female was referred because of progressive numbness of the left side of the chin and labial angle, which had started a few weeks previously. The numbness originally was limited to the left side of the lower lip and slowly increased in size to ultimately include the whole left side of the lower lip and chin region. The medical history revealed bronchial asthma since childhood, right-side breast cancer at the age of 55 years that was treated with mastectomy and chemotherapy, development of bone metastasis in the thoracic spine in 2004 that was treated with radiotherapy, and intake of bisphosphonate zoledronate over 5 years. The patient was edentulous, so the hypoesthesia could also have been caused by the compression of the mental nerve by her dental prosthesis. However, the numbness persisted over 4 weeks in which

Table 2 Details of the 10 Patients with Numb Chin Syndrome (NCS)

Patient	Age (sex)	Suspected pathology	Definitive pathology	Mandibular localization	Treatment	NCS/BRONJ delay from first cancer diagnosis	Survival
1	65 (F)	Metastasis of breast cancer	Bisphosphonate-related osteonecrosis (Zometa)	Mental region (left)	PROM and pelvic graft	–	Alive
2	62 (M)	Metastasis of plasmocytoma	Bisphosphonate-related osteonecrosis (Zometa)	Tooth 34 to mandibular ramus (left)	PROM and fibula graft	7 y	Alive
3	54 (F)	Periodontal disease	Adenoid cystic carcinoma of mandible	Region of tooth 34 to mandibular ramus (left)	PROM of the mandible (R1)	8 mo	Alive
4	54 (M)	Extraosseus manifestation of lymphoma	Extraosseus manifestation of lymphoma with bone invasion	Tooth 35	Palliative CT and RT	7 mo	4 mo
5	70 (F)	Metastasis of breast cancer	Bisphosphonate-related osteonecrosis (Zometa)	Teeth 36–37	PROM and fibula graft	14 y	Alive
6	54 (F)	Periodontal disease	Metastasis of uterine cancer	Teeth 44–47	PROM and fibula graft	3 y	Alive
7	69 (M)	Pressure on nerve by dental prosthesis	Metastasis of mediastinal cancer	Inside mandibular channel	Bonefos, 9 NC, EORTC, DOX, CYCLOPH	0 mo	6 mo
8	65 (M)	Neuropathy caused by metastasis	Bisphosphonate-related osteonecrosis (Zometa)	Teeth 47–48	PROM and fibula graft	18 mo	Alive
9	69 (F)	Mental neuropathy after augmentation	Nerve compression by Bio-Oss material	Mental foramen	Local treatment	–	Alive
10	39 (M)	Multiple sclerosis	Multiple sclerosis	Juxtacortical lesion	Methylprednisolone, disease-modifying drugs	–	Alive

BRONJ = bisphosphonate-related osteonecrosis of the jaw, M= male, F= female, RT= radiotherapy, CT= chemotherapy, S= surgical treatment, DOX = doxorubicin, CYCLOPH= cyclophosphamide, Zometa = zoledronate, Bonefos= clodronate, 9 NC = 9-Nitrocamptothecin, EORTC= European Organization for Research and Treatment of Cancer, PROM = partial resection of the mandible, R1 = R1 resection.

Fig 1 CT scans: *(a)* Axial CT-image destruction of the cortical bone (osteonecrosis) and a pathologic fracture in the left mandible body *(white arrows),* probably induced by bisphosphonate therapy. *(b)* Coronal CT image with a bone window showing the suspect area with osteolysis in the left mandible.

the patient did not wear the denture. Other neurologic symptoms, such as reduced smell and taste, or numbness of the left half of the palate, left tongue, or left upper lip, were absent. The numbness, in addition to the tumor history, suggested a mandibular metastasis. First an orthopantomogram (OPT) was performed, which demonstrated radiolucency on the left side of the mandible. Upon this discovery, computed tomography (CT) scans were ordered; these showed a fracture in the left-side mandibular corpus (Fig 1), not visible in the OPT, and soft tissue swelling surrounding the bone lesion with a liquid collection and contrast agent rim enhancement, suspicious of abscess formation. The patient history suggested a fracture due to metastasis followed by inflammation of the fractured region. Because of the suspicious diagnosis of an abscess, a blood sample was taken. It showed only a small increase of C-reactive protein (46 mg/L; normal range 0 to 5 mg/L) and an increased lactate dehydrogenase (299 U/L; normal range 120 to 250 U/L). Surgery revealed a necrotic bone area surrounding the fractured region and distinctive soft tissue swelling near the necrotic bone. The necrotic tissue was removed by partial resection of the mandibular body, and the resected area was reconstructed by means of an iliac crest graft. The histopathologic examination of the resected bone revealed osteonecrosis of the jaw, which was probably induced by the bisphosphonate therapy (bisphosphonate-related osteonecrosis of the jaw [BRONJ]). The patient has been followed up for 25 months and no relapse occurred.

Case 2

In November 2010, a 62-year-old male patient was referred by a neurologist to the Department of Oral and Maxillofacial Surgery, with chief complaints of dysesthesia and pain in the left chin area and mental region.

In 1998, the patient had been diagnosed with plasmocytoma with IgA-paraproteinemia type Kappa. In 1999, he received palliative chemotherapy. In 2002, therapy with bisphosphonate zoledronate (every 4 weeks) was initiated to reduce progression of the plasmocytoma. In 2010, because of the progression of the plasmocytoma, another cycle of palliative chemotherapy was initiated. A few weeks later, the patient was referred to the neurologist because of increasing numbness of his left chin area and mental region. At the time of the first visit, the patient presented total anesthesia of his left chin and mental region, as well as a lack of sensitivity of all teeth in the third quadrant. The examination of taste, lip movement, and left-side facial muscles was within normal limits. As well as the plasmocytoma, the previous medical history of the patient included high blood pressure and hypercholesterolemia. A blood sample, which is routinely performed in the department for all patients presenting with an unclear diagnosis, showed only increased uric acid (7.4 mg/dL, normal range 2.5 to 6.0 mg/dL) as well as reduced hemoglobin (9.6 g/dL, normal range 12.8 to 16.8 g/dL), erythrocytes (3.14 × 1,012/L, normal range 4.0 to 5.0 × 1,012/L), and hematocrit (28.2%, normal range 35% to 43%), pointing to anemia. An OPT showed a large radiolucent area, highly suspicious of plasmocytoma. To better evaluate the extent of the involved bone area, CT scans were acquired. These showed a large osteolytic area inside the mandible, including large parts of the left-side mandibular nerve canal.

NCS caused by the plasmocytoma was speculated, and it was decided to perform a partial resection of the mandible with simultaneous reconstruction using a fibula graft. The histopathologic examination of the excised tissue, however, did not confirm the working diagnosis of a plasmocytoma, but led to the diagnosis of extensive periosteal bone regeneration and BRONJ induced by bisphosphonate zoledronate, with sequestration and marginal clearance reaction of the bone with absence of malignancy. The follow-up period was 12 months, and no relapse occurred.

Case 3

In September 2010, a 54-year-old female patient was referred from the Department of Gynecology, where she was treated for breast cancer. During the treatment, the patient observed a progressively increasing swelling of the left cheek with recurrent pain episodes, and numbness of the lower lip and mental region. Extra- and intraoral examination showed a dysesthesia of the described region, as well as a sensory loss of teeth 31 to 35 and a subtle swelling with a local distension of the left-side vestibular gingiva. An OPT demonstrated radiolucency on the left side of the mandible. The subsequently performed CT scans of the head showed a corresponding hypodense bone lesion causing local bone destruction on the left side of the mandible. The medical history and clinical picture led to a working hypothesis of bone metastasis from breast cancer. Surgical treatment consisted of the resection of soft tissue and partial resection of the left mandible. The histopathologic examination revealed an adenoid cystic carcinoma infiltrating the left mandible with local destruction of the nerve canal. Due to incomplete resection of the tumor (R1 resection), another surgical intervention was performed 2 weeks later; this time the tumor could be excised totally. The follow-up period was 14 months with no relapse.

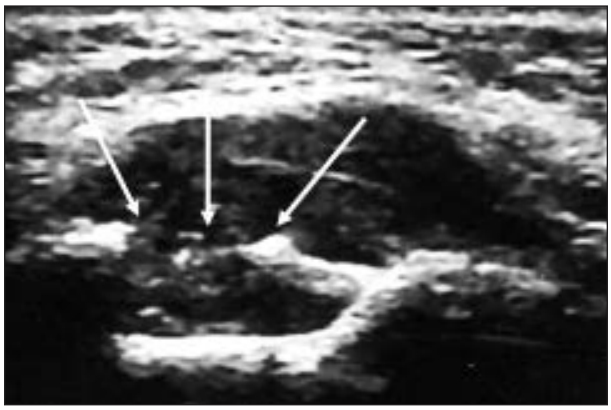

Fig 2 Sonographic investigation in the affected region showing destruction of the vestibular cortical bone by extraosseous manifestation of B-cell lymphoma *(white arrows)* in Case 4.

Case 4

In July 2010, a 54-year-old male patient, who had earlier been diagnosed with B-cell lymphoma (non-Hodgkin lymphoma), attended the authors' clinic in a wheelchair and in a reduced general condition. The patient had total anesthesia of the left chin, lower lip, left-side corner of the mouth, and mental region, including numbness of all teeth in the third quadrant. He reported a swelling of the left mandible for the last 4 weeks with recurrent pus emission. The oral examination revealed a soft swelling of the gingiva in the region of the mandibular left second premolar without fluctuation or pus flow. An OPT revealed radiolucency in the region of the second premolar. Because of the palpatory finding and the history of pus, sonographic investigation of the affected region by means of high-resolution ultrasound (HR-US) was carried out. An extraosseous manifestation of the B-cell lymphoma was suspected, inducing destruction of the left mandible, depicted on the vestibular side (Fig 2). Due to the patient's reduced general condition and mobility, it was impossible to perform magnetic resonance

imaging (MRI). Therefore, it was decided to perform cone beam computed tomography (CBCT), which showed an extraosseous soft tissue mass, slightly hypodense to the surrounding soft tissue, infiltrating the mandible and nerve canal. This finding was suggestive of B-cell lymphoma. To assess whether the suspected lymphoma was disseminated throughout the patient's body, a fluoro-deoxyglucose positron emission tomography (FDG PET)-CT scan was performed. This confirmed the CBCT diagnosis of a primary extraosseous manifestation of the lymphoma in the right maxillary sinus and detected further lesions in other parts of the body. Because of the disease progression and the patient's general health status, it was decided not to intervene surgically but to treat him by palliative chemotherapy and radiation therapy. Nonetheless, he died 4 months after the first visit.

Case 5

A 70-year-old female patient presented in October 2010 with a left-side mental and inferior dental hypoesthesia that had been present for approximately 3 months. The medical history revealed that the patient had been treated 17 years earlier for bilateral breast cancer with breast-conserving surgery in combination with radiation and chemotherapy. Fourteen years later, the right breast had to be resected completely due to local recurrence of the tumor. To prevent skeletal complications of the breast cancer, the patient was treated intravenously with bisphosphonate zoledronate every 3 weeks from 2003 to 2008. Clinical examination demonstrated numbness around the left side of the lower lip, which, in the medical history, initially increased slowly, affecting only some parts of the lower lip and the chin, but later included the whole left side of the lower lip and chin region as well as all teeth in the third quadrant. The OPT showed marked atrophy of the alveolar bone with an osteolytic lesion in the left molar region. A supplementary CT scan demonstrated a hypodense bone lesion, indicating osteolytic bone destruction, and bone scintigraphy revealed increased tracer uptake in the corresponding area. Surgical intervention with partial resection of the left mandible and reconstruction by fibula graft became necessary after the occurrence of a pathologic fracture in this region. The histopathologic diagnosis was osteonecrosis of the jaw, induced by zoledronate (BRONJ), with marked clearance reaction and secondary infection without any signs of malignancy. Further treatment was complicated by embolism of the pulmonary artery and retarded wound healing so that the patient left the hospital 5 weeks after surgical intervention. The latest follow-up was 4 weeks thereafter. Radiologic control of the operated region was done by panoramic view and showed good results.

Case 6

In 2007, a 54-year-old female patient presented with a chief complaint of paresthesia of the right mental region and lower lip, including pain in the right mandible. The paresthesia had begun some weeks earlier and was constant, while the pain had progressively increased. The medical history revealed that the patient had undergone chemotherapy for uterine carcinoma 2 years earlier and that she had been treated with bisphosphonate zoledronate in regular intervals of 4 weeks. Intraoral examination revealed a 20 × 5-mm^2-wide area of uncovered bone in the fourth quadrant as well as a reduced dental status. All orofacial muscle functions, including lip and tongue movement, were normal. Gustatory disturbances were not present. Based on the clinical findings and the patient's medical history, it was suspected that the numbness and pain were caused by a malignant process. Panoramic radiographs demonstrated an oval radiolucency in region 48. FDG PET-CT confirmed the presence of osteolytic bone destruction and showed increased tracer uptake. Scintigraphy confirmed the lesion in the mandible and revealed further lesions in other parts of the body (Fig 3). The patient underwent surgical osteotomy maintaining continuity of the mandible in the fourth quadrant in the premolar-molar area. The histopathologic diagnosis confirmed the working hypothesis of bone metastasis of the uterine carcinoma. The follow-up period was 16 months with no relapse.

Case 7

A 69-year-old edentulous male presented with a progressive hypoesthesia of the right chin and corner of the mouth, associated with intermittent phases of pain persistent over 4 weeks. The major pain was located at the mental foramen and radiated posteriorly along the nerve route. The patient's medical history included lung tuberculosis at the age of 23 years, a parotidectomy for pleomorphic adenoma at the age of 37 years, chronic obstructive pulmonary disease (COPD), and a stroke at the age of 58 years. The examination revealed an almost complete anesthesia of the right mental nerve region and an edentulous mandible. An OPT showed bilateral bone atrophy of the mandibular bone at the level of the mental foramina and the mandibular nerve canal. Numbness due to the compression of the mandibular nerve by the dental prosthesis was excluded because the patient had not been wearing the prosthesis for a long time. The CT scans of the head and neck and a plain radiograph of the chest did not reveal pathologic lesions. Nevertheless, the suspicion of a malignant space-occupying process in the mandible remained, and so it was decided to perform a surgical exploration in order not to miss a local cause. The surgical exposure

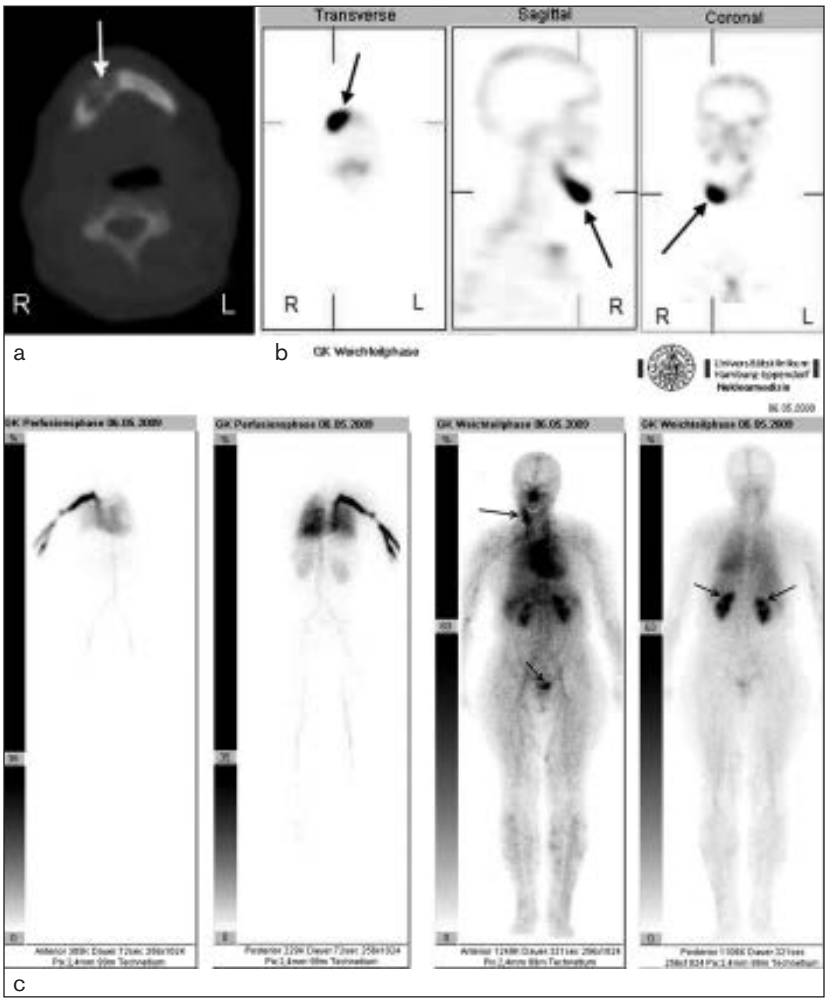

Fig 3 PET-CT scan of the head and whole-body scintigraphy in Case 6: *(a)* Axial CT image with a bone window showing cortical destruction of the right mandibular body in region 44 to 47 due to bone metastasis of the known uterine carcinoma *(white arrow). (b)* Scintigraphy of the head with technetium (Tc99m) showing increased uptake of technetium on the right side of the mandibular corpus *(black arrows),* where metastasis of the uterine carcinoma is located. *(c)* Whole-body scintigraphy performed with Tc99m showing increased uptake of Tc99m in the right side of the mandibular body *(black arrow),* uterus *(black arrow),* and both kidneys *(black arrows).*

of the inferior alveolar nerve showed a grayish mass invading the nerve and continuing its course up to the mandibular angle. Histologic examination following the surgical intervention revealed granulation and scar tissue, which supported the clinical hypothesis of a malignant process. While excising the whole tumor, the surgeon noted that it adhered to the nerve bundle but not to the bone. The nerve was displaced laterally. The final histopathologic examination of the excised material led to the final diagnosis of small-cell carcinoma, probably of pulmonary origin. The postoperatively performed CT scans of the chest displayed an extensive mediastinal tumor (dimensions: 7.6 $\times$ 6.2 $\times$ 8 cm^3) accompanied by multiple retrosternal, pretracheal, and subcarinal lymph nodes. Further evaluation by imaging and scintigraphy revealed metastases in the kidney and multiple bony lesions, suspected as bone metastases. The patient was initially treated by palliative chemotherapy and later with bisphosphonate clodronate once a month. Nonetheless, the patient died with evidence of tumor progression within 6 months after the initial diagnosis.

Case 8

In April 2008, a 65-year-old male patient was referred by a private dentist because of hypoesthesia of the right mental region and corner of the mouth, associated with intermittent phases of pain that had started 6 weeks before. The patient's medical history included prostate cancer, insulin-dependent diabetes mellitus (IDDM) since the age of 56 years, high blood pressure, and a heart attack at the age of 61 years treated with a stent implantation. The patient reported also that he was undergoing bisphosphonate therapy with zoledronate over the past 4 years. Clinical examination showed sensory loss of the right chin, lower lip, and mental region, including numbness of all teeth in the fourth quadrant. An OPT demonstrated radiolucency and bone loss in the fourth quadrant that extended up to the right-side mandibular angle (Fig 4). Since the exclusion of malignancy by OPT is not always possible, CT scans of the head and neck were performed. These demonstrated an extended osseous defect, indicative of osteonecrosis. The patient was surgically treated by necrectomy and

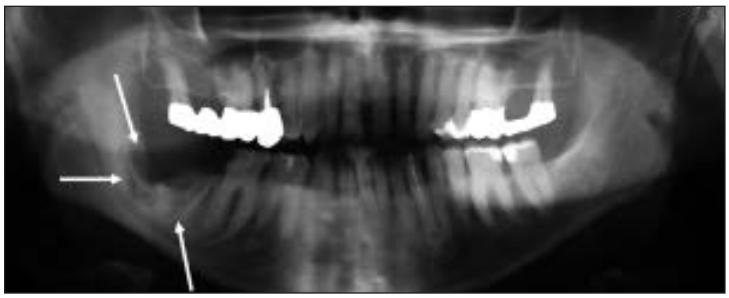

Fig 4 Panoramic radiography showing irregular radiolucency and osteolytic area in the right mandibular angle and region 47-48 because of BRONJ *(white arrows)* in Case 8.

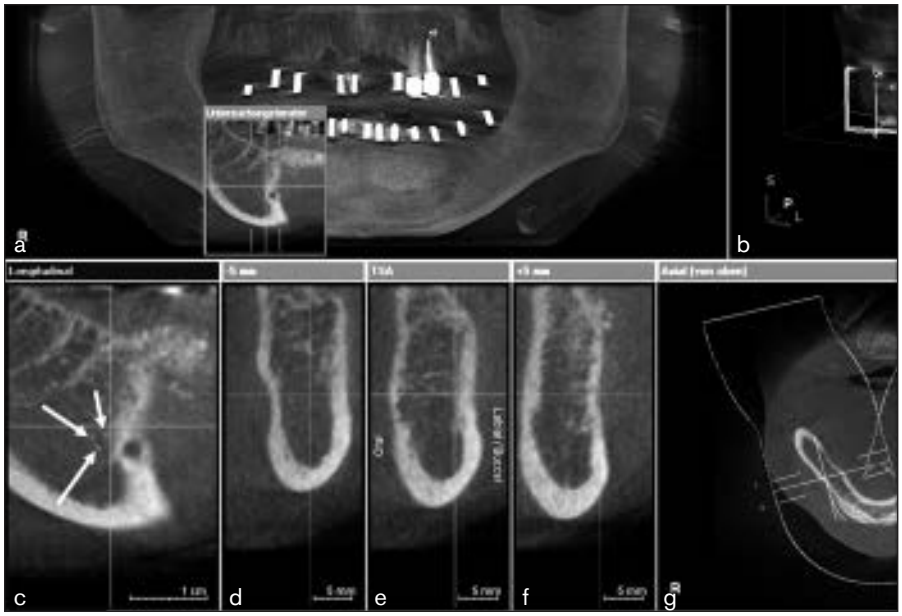

Fig 5 Postoperative CBCT of Case 9. *(a)* Panoramic view window with inset showing an enlargement of the mental foramen. *(b)* Parts of the 3D reconstruction of the CBCT (marks indicate the transversal cuts shown in *d, e,* and *f*). *(c)* Multiple particles directly in front of the mental foramen in close contact with the mental nerve *(arrows)*, causing NCS. *(g)* Axial view of the mandible with transversal slices in the middle.

modeling osteotomy. Intraoperative the bone showed a brown-gray color typical of osteonecrotic bone. The histopathologic examination of the excised bone led to the diagnosis of BRONJ, causative of the NCS. No relapse occurred in the 18-month follow-up.

Case 9

In June 2009, a 69-year-old female patient was referred to the Department of Prosthodontics for dental advice on implantology. The medical history did not reveal any medical contraindication for this therapy or that she had suffered from orofacial hypoesthesia or dysesthesia. The final treatment plan consisted of bone augmentation prior to implant placement. The augmentation procedure was performed in September 2009 with alloplastic material (Bio-Oss, Geistlich) stabilized by means of biodegradable barrier membrane (Bio-Gide, Geistlich) and tissue adhesive (Tisscol Duo S. Immuni 0.5 mL, Baxter). During the surgical procedure, the inferior alveolar nerve was exposed. Due to local anesthesia, no sensory testing was performed intraoperatively. On the following day, the patient complained of a 4 $\times$ 4.5 cm^2 area of numbness on the right side of her face. A postoperative CBCT demonstrated multiple radiopaque particles located directly in front of the mental foramen, in close contact with the mental nerve (Fig 5). Surgical revision was performed, and all particles along the nerve and mental foramen were removed. Nevertheless, a 3 $\times$ 3 cm^2 dysesthesia area remained and was still present at the end of the rehabilitation in 2011.

Case 10

A 39-year-old male patient was referred in June 2010 with left-side facial hypoesthesia involving the chin. These symptoms had occurred to a lesser extent in 2007, when a diagnosis of multiple sclerosis was first made. The hypoesthesia had worsened during the past week and had spread to the left shoulder and upper arm. Clinical examination showed a hypoesthesia for tactile and thermal stimuli and an allodynia in all trigeminal branches (including the chin) and the left arm. Additionally, mild paresis (MRC grade 4/5) of the left leg and brisk left-sided tendon reflexes were noticed. A cerebral MRI scan performed 8 days after the worsening of hypoesthesia showed three new supratentorial cerebral lesions (Fig 6), leading to the diagnosis of an acute flare-up of multiple sclerosis.

Methylprednisolone (1,000 mg) was given for 3 consecutive days. Five days later, the facial sensory deficits had remitted completely, while the left arm remained mildly hypoesthetic. Subsequently, a disease-modifying drug therapy with interferon beta was started. No flare-ups occurred in the 17 months of follow-up.

Discussion

In 1830, Charles Bell was the first to report on what is now known as NCS when he described a patient with numbness of the left side of the lower lip caused by a mandibular metastasis compressing the inferior alveolar nerve.[6] More than half a century later, Vincent reported hypoesthesia and anesthesia of the mental region after mandibular injuries.[7] Thereafter, the syndrome was described using several eponyms, in particular "Vincent's Syndrome" was frequently used. The name "numb chin syndrome" was probably not used until 1963, when Calverley and Mohnac described five patients with this symptom.[32] Since then, there have been several case reports in which "numb chin syndrome" was most commonly used to describe this symptomatology[2,11,15,16,33] compared to a small number of case reports, usually published by maxillofacial surgeons, that described this condition as "Vincent-Syndrome," mental neuropathy, or numb lip syndrome.[2,23,34]

This article used NCS as an umbrella term for a symptom caused by a large number of diseases. It is important to keep in mind that this term simply describes a symptom often related to a serious disease, and that as such it is not a diagnosis. Thus, the use of this term may be inappropriate, as it may lead one to overlook the underlying pathology.

NCS is a symptom that requires a high degree of alertness because it may be caused by a malignancy. Nonmalignant causes can be dental-related conditions such as a dental abscess, a radicular cyst, a dental-related tumor, or a mental nerve trauma from poorly fitting dentures.[2,35,36] Further nonmalignant causes are lesions of the mandibular bone due to trauma such as fractures, or to infections, such as osteomyelitis or odontogenic infections,[2,25,37] and iatrogenic injuries of the nerve, for instance due to mandibular augmentation, third molar surgery, orthognathic surgery, or, as demonstrated in Case 9 in the present article, due to procedures carried out for implant placement.[2,35,38,39] Dentists should be careful while using alloplastic material for bone augmentation close to the mental foramen. As far as orthognathic surgery, Jääskeläinen et al reported than more than 50% of patients who underwent this surgery had paresthesia in the distribution of the inferior alveolar nerve, including numbness of the chin and lower lip.[40] Finally, neurologic diseases, such as multiple sclerosis, Lyme disease, or strokes,[11,41,42] and less often diabetes mellitus,[43]sarcoidosis,[44] human immunodeficiency virus infection,[40] connective tissue disorders,[43,44] temporal arteritis,[45] demyelinating diseases,[46] or age-related mandibular atrophy[47] also may lead to NCS.

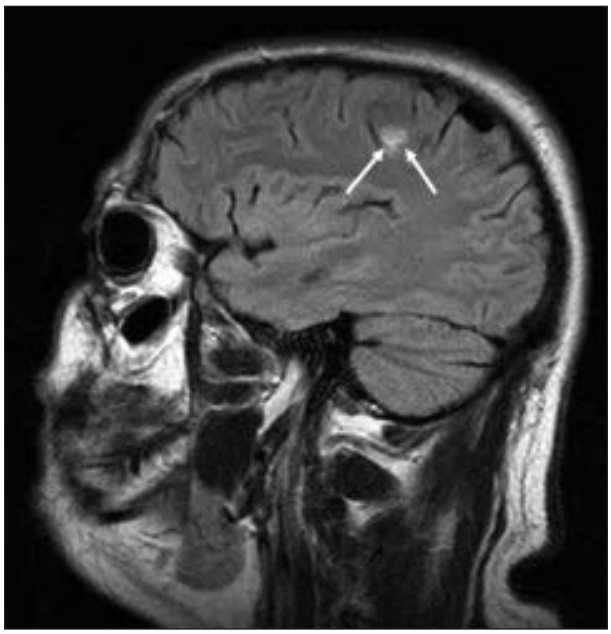

Fig 6 MRI scan: sagittal, T2-weighted image of Case 10 with multiple sclerosis with a juxtacortical lesion *(white arrows).*

Malignancies leading to NCS are particularly mandibular metastases of a primary tumor.[18] In women it is mostly a metastasis of breast cancer and in men of prostate cancer.[48–50] Other tumors that may metastasize to the mandible are lung, thyroid, renal, and stomach cancer,[15] In addition, a numb chin can be caused in rare cases by leptomeningeal spread of cancer, or from malignancies originating in blood cells, such as lymphoblastoma.[3,18,51]

Bone metastasis to facial bones is often localized to the mandible (> 75% of cases).[37,52] The prognosis for patients with NCS due to metastatic malignancy is poor, with a mean survival in many cases of only 6 months or less.[15,16,35] With a survival of nearly 12 months, the prognosis and median survival are somewhat better for patients presenting with a leptomeningeal than a localized mandibular involvement.[16,18,51]

This study presented four cases of patients with NCS resulting from a BRONJ located in the mandible. Bisphosphonates are used increasingly in recent years to protect bone from destruction by metastatic tumors.[53,54] In all four cases, it was hypothesized that the bone destruction was caused by metastasis, but, surprisingly, the histopathologic examination proved that it was associated with the BRONJ.

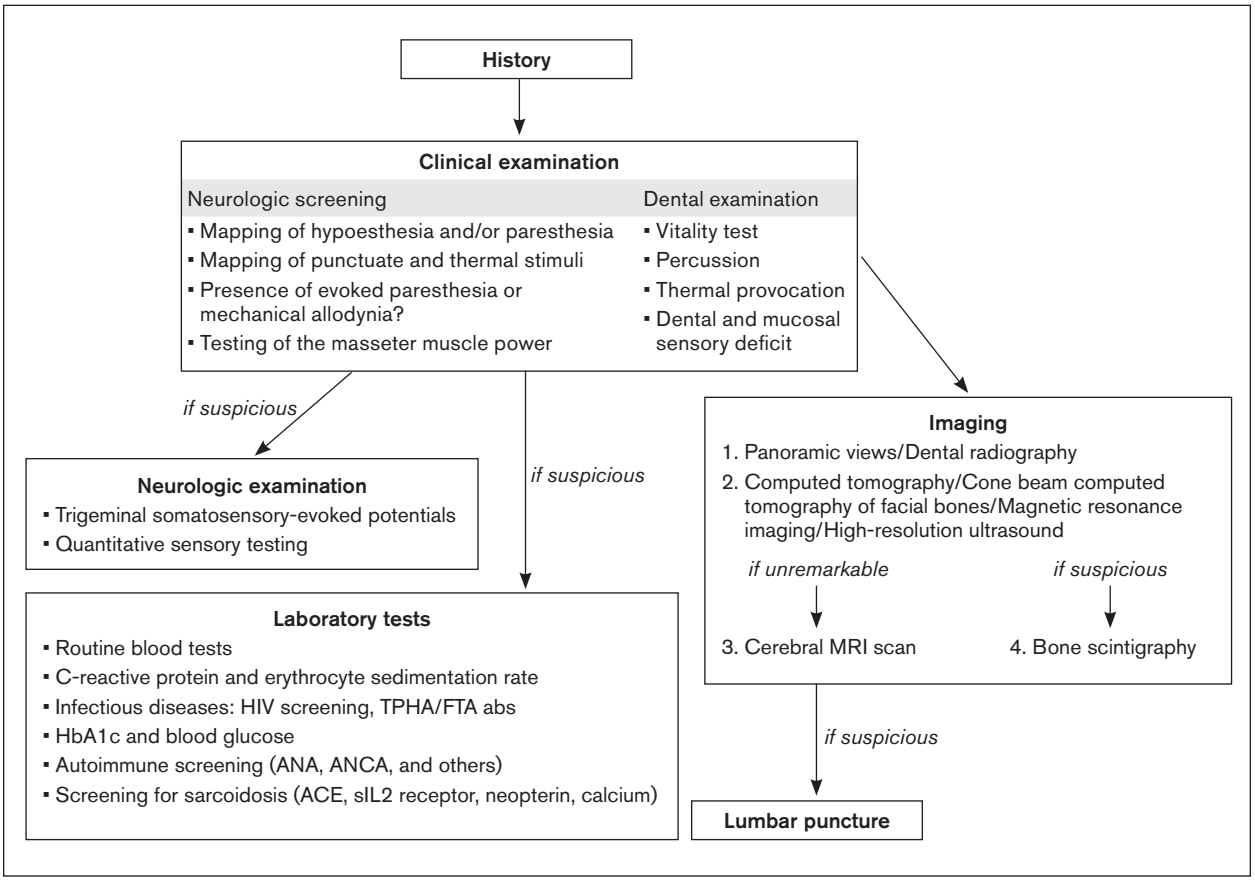

Fig 7 Diagnostic flow chart. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ACE, angiotensin converting enzyme; TPHA/FTA, treponema pallidum haemagglutination assay and fluorescent treponema antibody; HbA1c, glycated hemoglobin; sIL2, soluble interleukin 2.

In the literature, a number of mechanisms have been proposed to explain the NCS. These include trigeminal nerve involvement by metastases at the base of the skull, perineural infiltration of the mental or inferior alveolar nerve, compression of the nerve by mandibular metastasis,[23,51] leptomeningeal seeding, and meningeal carcinomatosis.[3,51,53–55] As demonstrated in case 4 in the present article, an extraosseous manifestation of lymphoma can also lead, although rarely, to NCS through osseous infiltration and destruction of the nerve canal. Neural invasion by several tumors, including various types of lymphomas, malignant melanomas, or carcinomas, has also been described in the literature.[3,15,17,19,21,28,31]

The large spectrum of NCS reflecting benign and malignant pathologies calls for the necessity of not minimizing the significance of NCS but to consider it as a serious problem whose diagnosis requires a thorough medical history, clinical examination, imaging, and when indicated, blood and cerebrospinal fluid analysis. As far as imaging, a review of the literature demonstrates that panoramic radiography is the first imaging method used in patients with NCS to evaluate the mandibular bone and the mandibular nerve canal.[12,36,51] However, soft tissue tumors and those inside the nerve canal may not be detected in panoramic radiographs,[15] thus the need for CT scans, CBCT, MRI, or scintigraphy. In addition, the diagnostic process may require thoracic or abdominal radiographs and, if needed, abdominal CT scans and MRI, PET-CT scans, sonography, and transcutaneous electrical nerve stimulation (TENS).[4,14–16,31,33,37,45,49,50] A diagnostic flow chart that may help the dentist and physician in diagnosing patients presenting with NCS is presented in Fig 7.

In the diagnostic process, involvement of the central nervous system should always be considered if sensory deficits exceed a purely peripheral pattern or spread to other regions. In addition, the presence of further neurologic deficits (such as paresis, ataxia, or impairment of further cranial nerves) requires a complete neurologic examination. Cases with peripheral neuropathies of the terminal branch of the mandibular nerve that are not attributable to the teeth and jaw need in-depth diagnostic assessment that includes a radiologic investigation of the central nervous system.

Once an underlying diagnosis is established, causative treatment is mandatory. Concomitant pain should be treated consequently with drugs, such as antiepileptics (gabapentin, pregabalin, lamotrigine),[36] antidepressants (amitriptyline, venlafaxine, duloxetine, carbamazepine), nonsteroidal analgesics, and topical therapeutics (capsaicin and lidocaine). Opioids should be restricted to cases with malignancy.

NCS should always be considered as being due to malignancy until proven otherwise.[36,56] Usually it represents a very advanced symptom of a metastatic tumor and is always indicative of disease progression.[15,16,36] The prognosis depends upon the underlying pathology.[23,25,35] In some cases, the primary malignancy is already known before the numbness is felt by the patient.[56] However, there are reports in the literature pointing to missed treatment as a consequence of minimizing the significance of the numbness or of being overlooked by practitioners and not urgently investigated.[16] For this reason, every practitioner should be aware that numbness in the innervation territory of the mandibular nerve must never be regarded as a trivial symptom.[56]

Acknowledgments

The authors report no conflicts of interest related to this study.

References

1. Colella G, Giudice A, Siniscalch G, Falcone U, Guastafierro S. Chin Numbness: A symptom that should not be underestimated: A review of 12 cases. Clin Invest 2009;337:407–410.
2. Smith SF, Blackman G, Hopper C. Numb chin syndrome: A nonmetastatic neurological manifestation of malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:53–56.
3. Laurencet FM, Anchisi S, Tullen E, Dietrich PY. Mental neuropathy: Report of five cases and review of the literature. Crit Rev Oncol Hematol 2000;34:71–79.
4. López-Jornet P. Mental nerve neuropathy as initial symptom of cancer. N Y State Dent J 2007;73:36–37.
5. Bell C. On the nerves of the face: Being a second paper on that subject. Philos Trans R Soc London 1829;119:317–330.
6. Bell C. The nervous system of the human body. London: Longman, 1830:64.
7. Vincent B. Sur un signe précoce de certaines ostéites du maxillaire inférieur se terminant par une nécrose. Revue Trimestrielle Suisse d'Odontologie 1896;6:148–163.
8. Pogrel MA. Permanent nerve damage from inferior alveolar nerve blocks—An update to include articaine. J Calif Dent Assoc 2007;35:271–273.
9. Hillerup S, Jensen R, Nerve injury caused by mandibular block analgesia. Int J Oral Maxillofac Surg 2006;35:437–443.
10. Pogrel MA, Thamby S. Permanent nerve involvement resulting from inferior alveolar nerve blocks. J Am Dent Assoc 2000; 131:901–907.
11. Oestmann A, Achtnichts L, Kappos L, Gass A, Naegelin Y. "Numb chin syndrome": First presenting syndrome of multiple sclerosis? [In German] Dtsch Med Wochenschr 2008;133: 76–78.
12. Ryba F, Rice S, Hutchison IL. Numb chin syndrome: An ominous clinical sign. Br Dent J 2010;208:283–285.
13. Abilleira S, Bowler JV. The numb chin syndrome as an early manifestation of giant-cell (temporal) arteritis: A case report. Headache 2005;45:1411–1413.
14. Mestoudjian P, Steichen O, Stankovic K, Lecomte I, Lionnet F. Sickle cell disease, a benign cause of numb chin syndrome. Am J Med 2008;121:e1.
15. Friedrich RE. Mental neuropathy (Numb Chin Syndrome) leading to diagnosis of metastatic mediastinal cancer. Anticancer Res 2010;30:1819–1822.
16. Divya KS, Moran NA, Atkin PA. Numb chin syndrome: A case series and discussion. Br Dent J 2010;208:157–160.
17. Massey EW, Moore J, Schold SC Jr. Mental neuropathy from systemic cancer. Neurology 1981;31:1277–1281.
18. Lossos A, Siegal T. Numb chin syndrome in cancer patients: Etiology, response to treatment, and prognostic significance. Neurology 1992;42:1181–1184.
19. Fenaux P, Lai JL, Miaux O, Zandecki M, Jouet JP, Bauters F. Burkitt cell acute leukaemia (L3 ALL) in adults: A report of 18 cases. Br J Haematol 1989;71:371–376.
20. Lynch TC Jr, McCloud TC, Harris NL. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case27-1994. A 41-year-old woman with neurologic abnormalities and an osteolytic lesion in the mandible. N Engl J Med 1994;331:107–113.
21. Newman NJ. Multiple cranial neuropathies: Presenting signs of systemic lymphoma. Surv Ophthalmol 1992;37:125–129.
22. Kuroda Y, Fujiyama F, Ohyama T, et al. Numb chin syndrome secondary to Burkitt's cell acute leukemia. Neurology 1991;41: 453–454.
23. Burt RK, Sharfman WH, Karp BI, Wilson WH. Mental neuropathy (numb chin syndrome). A harbinger of tumor progression or relapse. Cancer 1992;70:877–881.
24. Hashimoto N, Kurihara K, Yamasaki H, Ohba S, Sakai H, Yoshida S. Pathological characteristics of metastatic carcinoma in the human mandible. J Oral Pathol 1987;16:362–367.
25. Eppley BL, Snyders RV Jr. Mental neuropathy as a sign of distant malignancy: Report of cases. J Oral Maxillofac Surg 1992;50:1117–1119.
26. Vincent SD, Lilly GE, Hupp JR. Paresthesia of the mandibular division, trigeminal nerve. J Oral Maxillofac Surg 1993;51: 565–569.
27. Vincent SD, White RD. Progressive paresthesia of the trigeminal nerve. J Oral Maxillofac Surg 1993;51:70–74.
28. Sariban E, Donahue A, Magrath IT. Jaw involvement in American Burkitt's lymphoma. Cancer 1984;53:1777–1782.
29. Patton LL, McMillan CW, Webster WP. American Burkitt's lymphoma: A 10-year review and case study. Oral Surg Oral Med Oral Pathol 1990;69:307–316.
30. Anavi Y, Kaplinsky C, Calderon S, Zaizov R. Head, neck, and maxillofacial childhood Burkitt's lymphoma: A retrospective analysis of 31 patients. J Oral Maxillofac Surg 1990;48: 708–713.
31. Kuklok KB, Burton RG, Wilhelm ML. Numb chin syndrome leading to a diagnosis of acute lymphoblastic leukemia: Report of a case. J Oral Maxillofac Surg 1997;55:1483–1485.
32. Calverley JR, Mohnac AM. Syndrome of the numb chin. Arch Intern Med 1963;112:819–821.

33. Yoshioka I, Shiiba S, Tanaka T, et al. The importance of clinical features and computed tomographic findings in numb chin syndrome: A report of two cases. J Am Dent Assoc 2009; 140:550–554.
34. Al-Nawas B, Kämmerer PW. Osteomyelitis. Infections in the oral and maxillofacial area. Der MKG-Chirurg 2009;2:221–232.
35. Maillefert JF, Gazet-Maillefert MP, Tavernier C, Farge P. Numb chin syndrome. Joint Bone Spine 2000;67:86–93.
36. Evans RW, Kirby S, Purdy RA. Numb chin syndrome. Headache 2008;48:1520–1524.
37. Bar-Ziv J, Slasky BS. CT imaging of mental nerve neuropathy: The numb chin syndrome. AJR Am J Roentgenol 1997;168: 371–376.
38. Marinella M. Numb chin syndrome: A subtle clue to possible serious illness. Hosp Physician 2000;36:54–56.
39. Kipp DP, Goldstein BH, Weiss WW Jr. Dysesthesia after mandibular third molar surgery: A retrospective study and analysis of 1377 surgical procedures. J Am Dent Assoc 1980; 100:185–192.
40. Jääskeläinen SK, Peltola JK, Lehtinen R. The mental nerve blink reflex in the diagnosis of lesions of the inferior alveolar nerve following orthognathic surgery of the mandible. Br J Oral Maxillofac Surg 1996;34:87–95.
41. Sebor RJ. Numb chin syndrome: A case report. Compendium 1990;11:624–625.
42. Maillefert JF, Dardel P, Piroth C, Tavernier C. Mental nerve neuropathy in Lyme disease. Rev Rhum Engl Ed 1997;64:855.
43. Cruccu G, Agostino R, Inghilleri M, Manfredi M, Ongerboer de Visser BW. Mandibular nerve involvement in diabetic polyneuropathy and chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 1996;21:1673–1679.
44. Cohen DM, Reinhardt RA. Systemic sarcoidosis presenting with Horner's syndrome and mandibular paresthesia. Oral Surg Oral Med Oral Pathol 1982;53:577–581.
45. Benito-Leon J, Simon R, Miera C. Numb chin syndrome as the initial manifestation of HIV infection. Neurology 1998; 50:511–512.
46. Gallud L, Bagan JV, Cervello´ A, Jiménez Y, Poveda R, Gavalda C. Multiple sclerosis as first manifestation in oral and facial area: Presentation of four cases. Med Oral Patol Oral Cir Bucal 2006;11:141–145.
47. Gaver A, Polliack G, Pilo R, Hertz M, Kitai E. Orofacial pain and numb chin syndrome as the presenting symptoms of a metastatic prostate cancer. J Postgrad Med 2002;48:283–284.
48. Halachmi S, Madeb R, Madjar R, Wald M, River Y, Nativ O. Numb chin syndrome as the presenting symptom of metastatic prostate carcinoma. Urology 2000;55:286i-286iii.
49. Thompson A, Pearce I, Walton G, Payne SR. Numb chin syndrome: An unusual presentation of metastatic prostate cancer. BJU Int 2000;85:377–378.
50. Requena A, Riera-Mestre A, Formiga F, Vidaller A, Pujol R. Metastatic prostate carcinoma presenting as NCS in elderly people. J Am Geriatr Soc 2008;56:581–582.
51. Biasotto M. Numb chin syndrome as the presenting symptom of carcinomatous meningitis. Ann Oncol 2008;19:599–601.
52. Hirshberg A, Leibovich P, Buchner A. Metastatic tumors to the jawbones: Analysis of 390 cases. J Oral Pathol Med 1994; 23:337–341.
53. Sierra-Hidalgo F, de Pablo-Fernández E, Correas-Callero E, Villarejo-Galende A. Numb chin syndrome caused by bisphosphonates-induced osteonecrosis of the jaw. Rev Neurol 2009;49:190–192.
54. Young P, Finn BC, Bruetman JE. Numb chin syndrome by bisphosphonates. Eur J Intern Med 2008;19:557.
55. Baskaran RK, Krishnamoorthy, Smith M. Numb chin syndrome—A reflection of systemic malignancy. World J Surg Oncol 2006;4:52–54.
56. Narendra H, Ray S. Numb chin syndrome as a manifestation of metastatic squamous cell carcinoma of the esophagus. J Cancer Res Ther 2009;5:49–51.